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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,596	07/17/2000	Robert A. Macina	DEX-0075	8607

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	29

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/618,596	Applicant(s) MACINA ET AL.	
	Examiner Alana M. Harris, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *27* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Claims 1-5 are pending.

Claims 1-5 have been amended.

Claims 1-5 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' amendments to the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5 are broadly drawn to methods of determining the level of CSG within cells, tissues or bodily fluids in a patient in order to diagnose, stage and monitor colon

cancer, wherein the CSG is polynucleotide sequence, SEQ ID NO: 1 also referred to as Cln106, see page 3, lines 29 and 30. The term "CSG" encompasses polynucleotides due to degeneracy in genetic coding, variations in nucleotide sequence, which allegedly encodes the same polypeptide as the native polynucleotide sequence, see page 3, lines 20-23. These diagnostic methods include for example *in situ* hybridization techniques, radioimunnoassays, as well as reverse transcription polymerase chain reaction, see Assay Techniques section on pages 11-14.

The specification provides prophetic teachings of methods of diagnosing colon cancer, metastatic colon cancer, staging colon cancer, monitoring colon cancer, as well as monitoring the change in stage of colon cancer, see page 4, line 7-page 5, line 27. However, there is no evidence supporting the effectiveness of using any CSG in the claimed methods and more specifically the specification does not set forth enabling disclosure supporting the occurrence of SEQ ID NO: 1/ Cln106 Cln115 in colon cancer. The specification does not support the use of SEQ ID NO: 1 in methods of diagnosing colon cancer, colon metastases, staging and monitoring cancer cancer. There is no objective evidence in the specification that SEQ ID NO: 1, mRNA corresponding to SEQ ID NO: 1 or a polypeptide encoded by the said polynucleotide would be indicative of colon cancer or metastatic colon cancer. There is insufficient evidence noting the levels of CSG expression in biological samples comprising colon cancer samples versus matching normal adjacent samples. It is not reasonable to conclude that SEQ ID: 1 and the polypeptide encoded by the polynucleotide sequence would be effective in yielding a discriminate colon cancer diagnosis.

Applicants have not set forth any supporting evidence that suggests that SEQ ID NO: 1 is a unique tumor or molecular marker for colon cancer. Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive

value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section. Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

Furthermore, the specification does not support the use of SEQ ID NO: 1 in methods of diagnosing metastases, staging and monitoring colon cancer. There is no objective evidence in the specification that SEQ ID NO: 1, mRNA corresponding to SEQ ID NO: 1 or the protein encoded by SEQ ID NO: 1 would be useful as a marker of metastatic colon cancer. It is well known in the art that metastatic cancer cells have altered patterns of gene expression in comparison with the non-metastatic precursor cancer cell. For instance, metastatic breast cancer cells are negative for E-cadherin expression, while normal breast cells and non-invasive breast cells are positive (Oka et al, Cancer Research, 1993, vol. 53, pp. 1696-1701). Uteroglobin is another example of a gene product, which is expressed in a primary tumor but not in metastatic cells released from said tumor (Weeraratna et al, Clinical Cancer Research, 1997, Vol. 3, pp. 2295-2300). These references demonstrate the lack of correlation between gene expression in a primary tumor versus metastatic cells released from said primary tumor. Therefore, it cannot be predicted that the polynucleotides effective in the diagnosis of colon cancer would be expressed or effective in diagnosing metastatic colon cancer and consequently useful in the monitoring and staging the said cancer. The specification does not provide sufficient guidance and direction to implement SEQ ID NO: 1 and its

corresponding protein in methods of diagnosing colon cancer metastases, monitoring and staging colon cancer.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention. Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

5. Claims 1-5 are free of the art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
30 September 2003